



REVIEW ARTICLE: IN THE MANAGEMENT OF ORGANOPHOSPHORUS COMPOUND POISONING

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ABSTRACT

Organophosphorus compound (OPCs) is one of the most common causes of self-poisoning, which is seen in India. They are used as insecticides, herbicides, antihelminthics, ophthalmic agents, in chemical industry, and as nerve agents in chemical warfare. The OPCs which are in use since 1940s worldwide as insecticides have been a source of poisoning and continue to pose management problems. OPCs pesticide intoxications are estimated at 3 million per year worldwide with approximately 300000 deaths. Of these, about 1 million are accidental, and 2 million are suicidal poisonings. The fatality rate following deliberate ingestion of OPCs pesticides in developing countries in Asia is approximately 20% and may reach 70% during certain seasons and at rural hospitals. Medical treatment and management of organophosphorus pesticide poisoning is challenging, particularly in resource poor places where most of these patients present. Clinical practice is often less than ideal, with poor initial resuscitation and steadiness, and poor use of antidotes. Resuscitation, Decontamination, Specific antidote, and preventive measures continue to be the main stay of therapy. This review discusses the mode of action, clinical features, management, complications and postmortem findings along with its medicolegal aspects of OPCs intoxication.

KEYWORDS: Organophosphorus Poisoning, Pesticides, Organophosphorus compounds, Clinical Features, Management, Medicolegal Aspects, etc.

INTRODUCTION

Poisoning with organophosphorus (OP) compounds is a global public health problem. Poisons are subtle and silent weapons that can be easily used without violence and often, without arousing suspicion. Vast developments in the field of industries, medicine, and agriculture have led to the utilization of various new poisonous compounds. India predominantly being an agrarian country, wide use coupled with easy accessibility, i.e., "over the counter" availability of organophosphorus (OP) compounds, makes it the most common modality of poisoning.^[1] The incidence has steadily increased in the recent past and has reached a level in the developing countries, where it can be called a "social calamity." Common OP compounds used in agriculture are parathion, malathion, chlorpyrifos, and dichlorvos. OP compounds exist in a military setting as well in the form of nerve gas. Common among them are sarin, tabun, soman, and VX. OP agents or their metabolites cause toxicity by inhibiting the function of acetyl-cholinesterase an enzyme responsible for hydrolyzing and inactivating the neurotransmitter acetylcholine.^[2] Atropine is an established specific

antidote for organophosphorus poisoning (OPP). WHO recommends that a second type of antidote called pralidoxime (Pyridine-2-aldoxime methiodide, 2-PAM) should be given along with atropine.^[3]

Organophosphorus Compounds^[4,5,6]

They are esters of phosphoric acid or thiophosphoric acid. They are mixed with solvent – aromax – which has kerosene like smell. The examples are:

- (A) **ALKYL PHOSPHATES:** HETP (Hexa Ethyl Tetra Phosphate), TEPP (Tetra Ethyl Pyro Phosphate) (Tetron), OMPA (Octa Methyl Pyrophosphoramide), Dimefox, Isopestox, Malathion (Kill bug, Bugsoline), Sulfotepp, Dementon, Trichlorfon.
- (B) **ARYL PHOSPHATES:** Paraoxon, Parathion (Nitrostigmine) (Folidol, Kilphos, Ekato), Methyl-parathion (Metacide), Chlorthion, Diazinon (Diazion, Tik-20). They are available as dusts, granules and liquids.

ORGANOPHOSPHORUS COMPOUNDS	
Nerve Agents	
• G agents: sarin, tabun, soman	• V agents: VX, VE
Insecticides	
Dimethyl Compounds	Diethyl Compounds
• Dichlorvos	• Chlorpyrifos
• Fenthion	• Diazinon
• Malathion	• Parathion-ethyl
• Methamidophos	• quinalphos

Toxicokinetics^[7,8]

Organophosphates can be absorbed by any route including transdermal, transconjunctival, inhalational, across the GI and GU mucosa, and through direct injection. Plant absorbed OPCs through leaves and stems.

Distribution^[8]

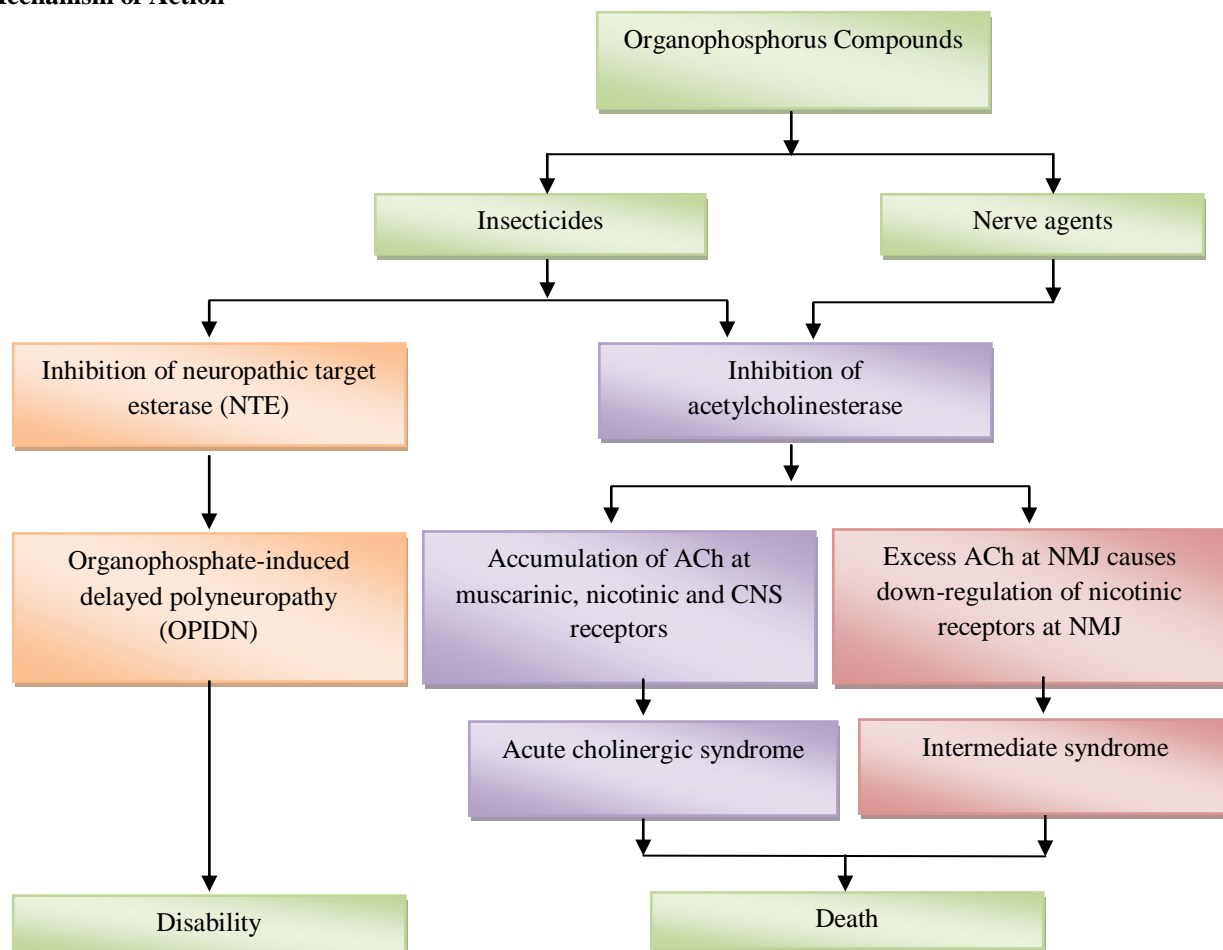
- Widely distributed in the body.
- Readily cross placenta.
- Lipophilic: Thus cross BBB. From deposits in fat and skin depending upon lipophilicity of individuals.

Metabolism^[8]

Main sites of metabolism are liver and blood. Minor sites are CNS, GIT, Kidney, Lung and Skin. Enzymes responsible are A-esterase's, Carboxylesterases (including B-esterase's), Fluorohydrolases and Microsomal oxygenases (cytochrome P₄₅₀ is most important). Metabolism can be done both activate and deactivate OP. Aryl OP require liver metabolism to become toxic.

Elimination^[8]

Excretion of metabolites occurs in the urine. Elimination is prolonged over a week.

Mechanism of Action^[9]**Clinical Features**^[10,11,12]**1. Acute Poisoning**

- **Muscarinic Effects** (hollow organ parasympathetic manifestations): Bronchoconstriction with wheezing and dyspnoea, cough, pulmonary oedema, vomiting, diarrhea, abdominal cramps, increased salivation, lacrimation, and sweating, bradycardia, hypotension,

miosis, and urinary incontinence. (features are described by word **SLUDGE** – Salivation, Lacrimation, Urination, Diarrhea, GIT cramps and Emesis, or **DUMBELS** – Diarrhea, Urination, Miosis, Bronchospasm, Emesis, Lacrimation and Salivation).

- **Nicotinic Effects** (Stimulation of pre-ganglionic sympathetic fibres): Fatigue, weakness, cramps, muscular twitching, dyspnea, cyanosis, pallor, hypertension, arrhythmias, paralysis of sphincters.
- **CNS Effects:** Restlessness, irritability, headache, tremor, drowsiness, delirium, slurred speech, ataxia, and convulsions. Death usually results from respiratory failure.

In some cases, only muscarinic or nicotinic or CNS effects are seen, but most cases show a combination of all three. Nicotinic effects are seen in 10 to 20% cases only.

- **Intermediate Syndrome:** In some cases after 1 to 4 days muscle weakness and paralysis characterized by motor cranial nerve palsies, weakness of neck flexor and proximal limb muscles, and acute respiratory paresis are seen due to prolonged cholinesterase inhibition and muscle necrosis. It does not respond to oximes or atropine.
- **Delayed Sequelae (OPIDP- OrganoPhosphorus Induced Delayed Polyneuropathy):** Delayed peripheral neuropathy can occur 1 to 5 weeks after exposure to certain compounds, such as parathion, malathion, trichlorfon, etc. It begins with paraesthesias and pain or cramps in the calves followed by ataxia, weakness, and toe-drop. It rapidly progresses to a flaccid paresis which can ascend similar to Guillain-Barre syndrome. Reflexes are diminished. The disease may progress for 2 to 3 months, and muscle wasting occurs.

2. Chronic Poisoning

- It usually occurs as an occupational hazard in agriculturists, especially those who are engaged in pesticide spraying of crops. Route of exposure is usually inhalation or contamination of skin. The following are the main features:
 - **Polyneuropathy:** paraesthesias, muscle cramps, weakness, gait disorder.
 - **CNS Effects:** Drowsiness, confusion, irritability, anxiety, psychiatric manifestations.

Fatal Dose^[13,14,15]

- TEPP 50 mg i/m or 100 mg orally.
- OMPA 80 mg i/m or 175 mg orally.
- Parathion 80 mg i/m or 175 mg orally.
- HETP 60 mg i/m or 350 mg orally.
- Malathion and Diazinon 1 gm orally

Fatal Period^[16,17]

Usually within 24 hours in untreated cases and within 10 days in treated cases, if unsuccessful.

Laboratory Diagnosis^[18]

1. Cholinesterase Level

- Depression of RBC cholinesterase level more than 50% of normal indicates organophosphate poisoning. The decrease is due to binding by phosphate group of pesticide. It is better parameter than plasma cholinesterase.

- Depression of plasma (serum) cholinesterase activity more than 50% of normal indicates organophosphate poisoning. This test is not specific as plasma cholinesterase activity is also depressed in cirrhosis of liver, neoplasia, malnutrition, septicemia due to burn, obstructive jaundice.

2. Colorimetric method

- 1 ml urine sample is taken and 1 ml of NBB [45% in acetone (4-nitrobenzyl) pyridine] added and mixed for 30 seconds in vortex mixer. The mixture is heated at 100°C for 20 minutes. Organophosphate insecticide shows a characteristic purplish blue color that can be read using spectrophotometer.
3. P-nitrophenol test.
 4. Paper chromatography.
 5. Thin layer chromatography (TLC).
 6. Gas chromatography (GC).
 7. Gas chromatography-mass spectrometry (GC-MS).
 8. High performance liquid chromatography (HPLC).
 9. ECG may show right axis deviation, ST segment depression and T-wave inversion.

Confirmatory Diagnosis^[19]

Diagnosis may be confirmed by giving 2 mg of atropine. In a normal person this causes marked atropinisation, but in case of poisoning by organophosphorus, symptoms are relieved without atropinizing. Estimations of cholinesterase are confirmatory.

Differential Diagnosis^[20]

Gastroenteritis, asthma, heat prostration, influenza, exhaustion, hypoglycemia, pneumonia, carbon monoxide poisoning, narcotic overdose, ketoacidosis, sepsis, meningitis, encephalitis, Reye's syndrome, neurologic disorders and subdural or epidural hematoma.

Causes of Death^[21]

- Asphyxia due to paralysis of respiratory muscles.
- Cardiac arrest.
- Pulmonary edema.
- Cerebral edema.

Management^[22, 23,24]

The patient is treated according to the severity of the symptoms. Among all approaches, external decontamination and early atropinization are only likely to be beneficial in OPCs poisoning, and oxime used is unlikely to be effective.

1. Decontamination

- Patient is removed from source of exposure, stripped of his clothes and the skin flushed with water.
- Doctor and nurses should be protected with water-impermeable gowns, masks with eye-shields, and use double gloves while handling the patient.
- **Gastric lavage:** It should only be undertaken once the patient is stable. Gastric emptying should be done with continuous suction via a nasogastric tube

with 1:5000 KMnO₄. Activated charcoal should be administered in doses of 1 g/kg.

- Patients with ocular exposures should have copious eye irrigation with normal saline or lactated Ringer's solution. If these are not available, tap water can be used.

2. Maintain ABC (Airway, Breathing and Circulation)

Care of the airway, breathing, and circulation ought to be started first. Most important step as copious secretions may be blocking airways (cause of death in OPCs poisoning is respiratory failure). (i) Clean airway of secretions. (ii) Endotracheal intubation. (iii) Administration of oxygen. (iv) Positive pressure ventilation. (v) Tracheostomy if necessary.

3. Antidotes

(i) **Mechanical antidote:** Activated charcoal 1 gm/kg of body weight.

(ii) **Physiological antidote:** Atropine sulphate, Pralidoxime (2-PAM).

❖ **Atropine Sulphate:** Atropine blocks the muscarinic manifestations and has no effect on nicotinic receptors (on muscle weakness or paralysis) and does not affect the rate of regeneration of inhibited AChE.

- **Dose:** 2–4 mg IV (0.05–0.2 mg/kg in children) repeated after every 5–15 minutes (min) till atropinization, the dose should be adjusted to maintain this effect for at least 24 h (maintenance dose: 0.02–0.05 mg/kg).

- Mild to moderate atropinization includes dryness of tongue, reduced secretion of oropharyngeal and bronchial tree, tachycardia and flushing. Mydriasis is an early response to atropine and is not a therapeutic end point. A common failure of therapy is not maintaining adequate atropinization.

- Glycopyrrolate may be substituted, if there is no evidence of central toxicity.

❖ **Pralidoxime (2-PAM):** A nucleophilic oxime, most effective when treatment is started early and if used within 48 h, and helps in regenerating AChE associated with skeletal muscle neuromuscular junctions. Dose: 1–2 g IV (20–40 mg/kg) over 5–20 min dissolved in 0.9% normal saline solution, may be repeated at 1–2 h if muscle weakness is not relieved, and again after 8–10 h. Transient dizziness, blurred vision, diplopia and elevations in diastolic BP may occur depending on the administration rate. Alternatively, continuous infusion (200–400 mg/h) of 2-PAM is more effective because of shorter duration of action of single dose.

4. Diazepam

Addition of diazepam for treatment of seizures and neuropathy improves survival (must not be used with other CNS depressants). It decreases the cardiac and

brain morphologic damage resulting from OPCs seizures. Dose: 0.5–2 mg IV every 15 min.

5. Supportive care

- Foot-end of the bed is raised to ensure drainage of respiratory secretions.
- Suction as required, to remove respiratory secretions.
- Treat bronchospasm with atropine and not bronchodilators.
- Intubate in case of respiratory distress.
- The use of other medication, including opioids for sedation may worsen CNS manifestations and the degree of respiratory depression.
- Dextrose: 2–4 ml/kg of 50% dextrose IV.
- Antibiotics to prevent pulmonary infection.
- Vitamin-K may also be given.

Preventive Measure^[25]

- Protective clothing consisting of overall of white cotton, a white cloth hood to cover the head and neck, rubber apron, gloves and boots, eye-shields and respirator.
- The face and the hands should be thoroughly washed after spraying with soap water or he should take a bath on the farm itself.
- Not more than 2 hours spraying a day should be done by a worker, and he should not work for more than 6 successive days on spraying. A person suffering from cold, bronchitis, etc. should not be engaged in spraying operation.
- The workers should be properly instructed and their work supervised.
- The workers should not smoke, chew or drink in the spraying area.
- Spraying machines, tanks, containers, hoses, etc. should be thoroughly washed at the end of the work and before repairs are carried out.
- Stop spraying immediately if you get a rash or feel sick, if your eyesight troubles you or you begin to sweat more than usual or feel unusually thirsty or have a headache.

Complications^[26]

Immediate	Delayed
Pulmonary edema	Paralysis
Aspiration pneumonia	Neurotoxicity
Chemical peritonitis	Guillain-Barre syndrome
Hyper/Hypoglycemia	
Coagulation abnormalities	

Postmortem Findings^[27,28]

External

- Kerosene-like smell from nostrils and mouth.
- Cyanosis of lips, fingers and nose.
- Constricted pupils.
- Deep postmortem staining.

- Congested face.
- Frothy discharge, often bloodstain from the nose and mouth.

Internal

- Mucosa of the stomach and intestine is congested.
- Stomach content may give kerosene-like smell.
- Respiratory passages are congested, contain frothy hemorrhagic exudates.
- Petechial hemorrhage may be present subpleurally.
- Edema and congestion of the lungs and other visceral organs.
- Features of toxic myocarditis had also been reported.
- Edema of brain.

Medicolegal Aspects^[27,28]

- Hospitalizing all symptomatic patients for at least 4-6 days following resolution of symptoms is recommended, because of the risk of development of respiratory depression or intermediate syndrome after resolution of an acute crisis.
- The symptoms of OPCs poisoning can mimic other toxidromes and diseases. The clinician must keep in mind that misdiagnosis is a potential medico-legal pitfall.
- Accidental and occupational poisoning occurs in manufacturers, packers, sprayers and in children. OPCs residue in fruits and vegetables may not induce toxic features, but could affect the health.
- Suicidal poisoning is common in our country, both in rural and urban areas. OPCs are also common suicidal agents in Pakistan, Sri Lanka and the other Asian and South East Asian countries.
- Homicidal poisoning does not occur due to detectable smell of the diluents, and signs and symptoms appear rather early.
- It is used for chemical warfare, e.g. nerve gases.

CONCLUSION

A lot of development has occurred in the field of management of OPCs poisoning. Recent investigations have revealed more understanding on the basic principles of treatment, and newer medications are now available for the management of OP poisonings. However, further studies are required to find out more effective treatments for the severe OPCs poisonings. Prevention still appears to be the best modality of management. Appropriate legislations and pesticide control are recommended for the developing countries to prevent occupational, accidental, and intentional poisonings. Hopefully, this new guidance will include the use of novel antidotes that will reduce the case fatality from pesticide poisoning, and therefore reduce the worldwide number of deaths from self-harm.

REFERENCES

1. Malik GM, Mubarik M, Romshoo GJ. Organophosphorus poisoning in the Kashmir Valley, 1994-1997, *N Engl J Med*, 1998; 338: 1078.
2. Chugh SN, Agarwal N, Dabla S. Comparative evaluation of "atropine alone" and atropine with pralidoxime in the management of organophosphorus poisoning. *J Indian Acad Clin Med*, 2006; 6: 33-7.
3. du Toit PW, Müller FO, van Tonder WM, Ungerer MJ. Experience with the intensive care management of organophosphate insecticide poisoning, *S Afr Med J*, 1981; 60: 227-9.
4. S. K. Singhal, Singhal's Toxicology at a Glance 9th reprint edition-2017, The National Book Depot Mumbai-400012, p-101.
5. K. S. Narayan Reddy, The Essentials of Forensic Medicine and Toxicology 34th edition-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-484.
6. Stanley Davidson, Davidsons Principles and Practice of medicine 20th reprint edition-2008, Churchill Livingstone Elsevier Publisher USA, p-216.
7. V V Pillay, Textbook of Forensic Medicine & Toxicology 18th edition-2017, Paras Medical Publisher Hyderabad-500095, p-648.
8. Anil Aggrawal Forensic Medicine and Toxicology for MBBS 1st edition-2016, Avichal Publishing Company Sirmour-173030, (HP), p-494.
9. Stanley Davidson, Davidsons Principles and Practice of medicine 20th reprint edition-2008, Churchill Livingstone Elsevier Publisher USA, p-217.
10. V V Pillay, Textbook of Forensic Medicine & Toxicology 18th edition-2017, Paras Medical Publisher Hyderabad-500095, p-648.
11. S. K. Singhal, Singhal's Toxicology at a Glance 9th reprint edition-2017, The National Book Depot Mumbai-400012, p-101-102.
12. K. S. Narayan Reddy, The Essentials of Forensic Medicine and Toxicology 34th ed-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-485-486.
13. Rajesh Bardale, Principles of Forensic Medicine & Toxicology 2nd edition-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-551.
14. K. S. Narayan Reddy, The Essentials of Forensic Medicine and Toxicology 34th ed-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-485-486.
15. Jaising P Modi, Modi A Textbook of Medical Jurisprudence and Toxicology 26th edition-2018, Lexis Nexis publication Gurgaon-12202, Haryana, section-2, p-61-62.
16. Gautam Biswas, Review of Forensic Medicine and Toxicology 4th edition-2019, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-608.
17. Jaising P Modi, Modi A Textbook of Medical Jurisprudence and Toxicology 26th edition-2018,

- Lexis Nexis publication Gurgaon-12202, Haryana, section-2, p-61-62.
18. Rajesh Bardale, Principles of Forensic Medicine & Toxicology 2nd edition-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-552-553.
 19. K. S. Narayan Reddy, The Essentials of Forensic Medicine and Toxicology 34th ed-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-485-486.
 20. Gautam Biswas, Review of Forensic Medicine and Toxicology 4th edition-2019, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-608.
 21. S. K. Singhal, Singhal's Toxicology at a Glance 9th reprint edition-2017, The National Book Depot Mumbai-400012, p-102.
 22. Gautam Biswas, Review of Forensic Medicine and Toxicology 4th edition-2019, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-608-609.
 23. Anil Aggrawal Forensic Medicine and Toxicology for MBBS 1st edition-2016, Avichal Publishing Company Sirmour-173030, (HP), p-497-498.
 24. V V Pillay, Textbook of Forensic Medicine & Toxicology 18th edition-2017, Paras Medical Publisher Hyderabad-500095, p-650-651.
 25. K. S. Narayan Reddy, The Essentials of Forensic Medicine and Toxicology 34th ed-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-487-488.
 26. Gautam Biswas, Review of Forensic Medicine and Toxicology 4th edition-2019, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-610.
 27. Rajesh Bardale, Principles of Forensic Medicine & Toxicology 2nd edition-2017, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-553.
 28. Gautam Biswas, Review of Forensic Medicine and Toxicology 4th edition-2019, Jaypee Brothers Medical Publishers (P) Ltd New Delhi-110002, p-610.